The hearing brain in males and females

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Chapter 3

Functional sex differences in human primary auditory cortex

Abstract

We used Positron Emission Tomography to study cortical activation during auditory stimulation and found functional sex differences in the human primary auditory cortex (PAC). Regional cerebral blood flow (rCBF) was measured in 10 male and 10 female volunteers while listening to sounds (music or white noise) and during a baseline (no auditory stimulation). We found a sex difference in activation of the left and right PAC when comparing music to noise. The PAC was more activated by music than by noise in both men and women. But this difference between the two stimuli was significantly higher in men than in women. To investigate whether this difference could be attributed to either music or noise, we compared both stimuli with the baseline and revealed that noise gave a significantly higher activation in the female PAC than in the male PAC. Moreover, the male group showed a deactivation in the right prefrontal cortex when comparing noise to the baseline, which was not present in the female group. Interestingly, the auditory and prefrontal regions are anatomically and functionally linked and the prefrontal cortex is known to be engaged in auditory tasks that involve sustained or selective auditory attention. Thus we hypothesize that differences in attention result in a different deactivation of the right prefrontal cortex, which in turn modulates the activation of the PAC and thus explains the found sex differences in the activation of the PAC.

Our results suggests not only that sex is an important factor in auditory brain studies but also that sex differences can already be present at the level of the primary auditory cortex.

Introduction

Previously, investigators tried to relate sex differences in behavior and cognition to differences in brain anatomy, function or connectivity. A well-documented example of sex differences in the brain is the difference in overall brain size. We now know that the size of the male brain is on average 8-10 % larger than the female brain (Dekaban and Sadowsky, 1978;Lynn, 1994;Peters et al., 1998). It is also thought that, compared to the female brain, there is more hemispheric asymmetry in the anatomy of the male brain (Kulynych et al., 1994;Amunts et al., 2000;Good et al., 2001;Kovalev et al., 2003), which is supported by the finding that in the male brain, functions are represented more unilaterally (Hiscock et al., 1994, 1995;Kansaku and Kitazawa, 2001; Mcglone, 1980; Wisniewski, 1998).

Sexual dimorphism has also been reported for the anatomy and function of the auditory cortex. For example, Rademacher et al. (2001a) reported that both left and right primary auditory cortices (PAC: Brodmann's area 41, Brodmann, 1909) are larger in females than in males, although an earlier study found no differences (Kulynych et al., 1994). Anatomical reports also show larger and more symmetrical auditory association cortices (Brodmann areas 42, 22) in females than in males (Kulynych et al., 1994;Harasty et al., 1997). However, many studies emphasize that there is intersubject variability regarding the size and location of the primary and secondary auditory cortex (Penhune et al., 1996;Leonard et al., 1998;Shapleske et al., 1999;Morosan et al., 2001;Rademacher et al., 2001b, 2002).

Functional sex differences in auditory brain areas are widely studied in the light of language processing. Females depend less on their left hemisphere for language processing than males in some studies (Shaywitz et al., 1995;Jaeger et al., 1998), whereas in other studies the opposite was found (Obleser et al., 2001) or no sex difference could be detected (Frost et al., 1999; Sommer et al., 2004). Whether a sex difference in language processing can be detected might depend on the nature of the task (Kansaku and Kitazawa, 2001). In all of these studies, however, the focus is mainly on functional sex differences in higher order (associative) brain areas, thereby ignoring possible sex differences in primary auditory cortices. In the present study, we investigated potential sex differences in the activity of the primary auditory region, using different auditory stimuli.

Material and Methods

Subjects

Twenty healthy, right-handed volunteers participated in this study (10 males, 10 females). Mean age for men was 23 years (range 20-25) and for women 22 years (range 19-27). All volunteers gave written informed consent according to the Declaration of Helsinki and the Medical Ethics Committee of the University Medical Center Groningen approved the study. None of the subjects had any history of psychiatric or neurological disorders. Prior to the scanning, subjects were tested for their hearing thresholds using standard audiometric measures. All subjects had normal hearing thresholds (< 20 dBHL, 0.25-8 kHz) and only small intersubject variations in hearing thresholds were observed.

Data Acquisition

Regional cerebral blood flow (rCBF) was measured using radioactive water ([^{15}O]-water, halflife 122 sec) as a tracer. A Siemens Ecat Exact HR+ PET scanner, operated in three-dimensional mode with a 15,5 cm axial field of view, acquired 63 slices simultaneously. Each subject was scanned 12 times to measure the distribution of [^{15}O]-water with a 10 minutes interval between two scans to allow for decay. Each scan was performed after an intravenous bolus injection of 500 MBq of [^{15}O]-water per scan. Except for the first scan, scanning started 30 s prior to injection, to account for background activation. Scanning continued for 120 seconds. The activity measured during this period was summed and used as a measure of rCBF. A scan specific calculated attenuation correction was performed to minimize interscan displacement-induced variance (Reinders et al., 2002). All subjects were scanned at fixed times on fixed weekdays and male and female subjects were addressed to the scan dates randomly.

Experimental design

Three conditions were used in this study: baseline (no auditory stimulation), white noise (at an intensity level of 75 dBSL) and music (music of the movie “The Piano” at 75 dBSL). Both music and noise have a wide frequency range, stimulating a large number of haircells in the cochlea and hence a large portion of the cortical auditory areas, but noise has a continuous and uniform frequency spectrum whereas music is a dynamic stimulus. Each condition was presented four times in a random order. For stimulus presentation we used a clinical audiometer (Interacoustics, model AC30), a Tandberg Educational taperecorder and E.A.RTone® 3A insertphones (with E.A.Rlink™ eartips), which have a flat frequency response between 100 and 4000Hz, measured in a Zwislocki-coupler. Stimuli were presented binaurally. Ten seconds before injection of radioactive water, the stimulus was started. Because the tracer reaches the brain approximately 10 seconds after injection, subjects were exposed to the stimulus for 20 seconds before the distribution of $[^{15}O]$-water in the brain starts. Subjects were instructed to close their eyes, not to move during the scans and to listen to the auditory stimuli. Before each scan we informed the volunteers that the scan was about to start. Immediately after each scan the volunteers were questioned about the scan (did they hear the stimulus, were they uncomfortable or distracted). During scanning we monitored the subjects with infrared cameras.

Data analysis

The 2000 version of Statistical Parametric Mapping (SPM2: software from the Wellcome Department of Cognitive Neurology, London, UK) was used for spatial transformations (realignment, transformation into standard stereotactic space and smoothing with an isotropic Gaussian kernel of 8 mm FWHM) and statistical analysis (Friston et al., 1995). An ANOVA estimated the following parameters: two groups (male and female), three conditions (baseline, noise and music) and the mean perfusion to normalize for global flow differences (Multigroup, conditions and covariates). Each scan was scaled to a mean global activity of 50 ml/100ml/min. Hypotheses about regionally specific condition effects were tested comparing the estimates, using linear compounds or contrasts. The resulting set of voxel values for these contrasts constituted the associated SPM of the t-statistics.

The significance threshold used for the analysis of the two groups separately (male-female) $p<0.05$ False Discovery Rate (FDR) corrected for multiple comparisons, Genovese et al., 2002) with an extent cluster threshold of more than 8 voxels. We used AMIDE software (http://amide.sourceforge.net/) for color scaling and display of the results on the anatomical MRI template of SPM2. For maximum statistical sensitivity and for testing the significance of the sex related differences, we conducted a region of interest (ROI) analysis in our a-priori hypothesized areas, i.e. the left and right PAC, using the SPM Anatomy toolbox (Eickhoff et al., 2005) and MarsBaR toolbox (MARSeille Boîte À Région d'intérêt, Tzourio-Mazoyer et al., 2002). Specifically, we created anatomical ROI's based on the three-dimensional probabilistic cytoarchitectonic maps from the SPM Anatomy toolbox brains (Morosan et al., 2001; Rademacher et al., 2001b; Eickhoff et al., 2005). To compensate for differences in stereotactic space between SPM and the Anatomy toolbox, a linear transformation was applied to the anatomical ROI's. MarsBaR was then used to conduct the statistical analyses on these ROI's. The statistical procedure in MarsBaR is the same as in SPM, but instead of analyzing on a voxel-by-voxel basis like SPM does, all voxels in a region are averaged and hence inferences about the whole region can be made. Also in MarsBaR, contrasts were considered significant at $p<0.05$.

Results

Music versus noise

For this contrast, in females the SPM-analysis resulted in significant bilateral activation clusters with a maximal significant voxel in the secondary auditory areas. In men much larger bilateral clusters were found covering not only the secondary auditory areas but also the PAC (Figure 1A and Table 1). This indicates that males have a much larger activation in the PAC during music than during noise. The voxel-wise analysis of SPM did not reveal any significant activation differences between the two sexes.

The region of interest analysis in the PAC showed that females do have a larger activation in the PAC during music than during noise (p-values 0.005 and 0.001 for the left and right PAC respectively). But the difference between music and noise is much smaller than in males in both the left and right PAC (p-values 0.016 and 0.008 respectively, Table 2, Figure 2). No significant deactivations were found (i.e. noise versus music).

To determine whether this sex difference can be attributed to the processing of either music or noise, we compared these two stimuli with a baseline without experimental auditory stimulation.

Music versus baseline

For this contrast, the SPM-analysis showed both in males and females large comparable activation clusters covering primary and secondary areas (Figure 1B and Table 1). The ROI analysis showed that there were no significant differences in the activation of the PAC between both sexes for this contrast (Table 2, Figure 2). Again, no significant deactivations were found (baseline versus music).

Noise versus baseline

Comparing noise to the baseline, the SPM-analysis showed two significant bilateral activation clusters with maxima in the PAC for the female group. In contrast, no significant activations were found in the male brain at a corrected level of $p<0.05$ (Figure 1C and Table 1). Only when the data were analyzed at an uncorrected threshold of $p<0.01$, a small activation appeared in the PAC of males, primarily on the right side (Figure 3). The ROI-analysis confirmed in men the involvement of the PAC while processing noise, showing significant bilateral increases of bloodflow, but these activations were significantly less than in women in the left (0.042) and right PAC ($p=0.034$) (Table 2).

The voxel-wise analysis of SPM also revealed a significant deactivation in the male group. This deactivation was located in the right dorsolateral part of the prefrontal cortex extending to the posterior part of the middle frontal gyrus, covering primarily BA 9 (Figure 4 and Table 1). In contrast, no significant deactivation was found in the female group.

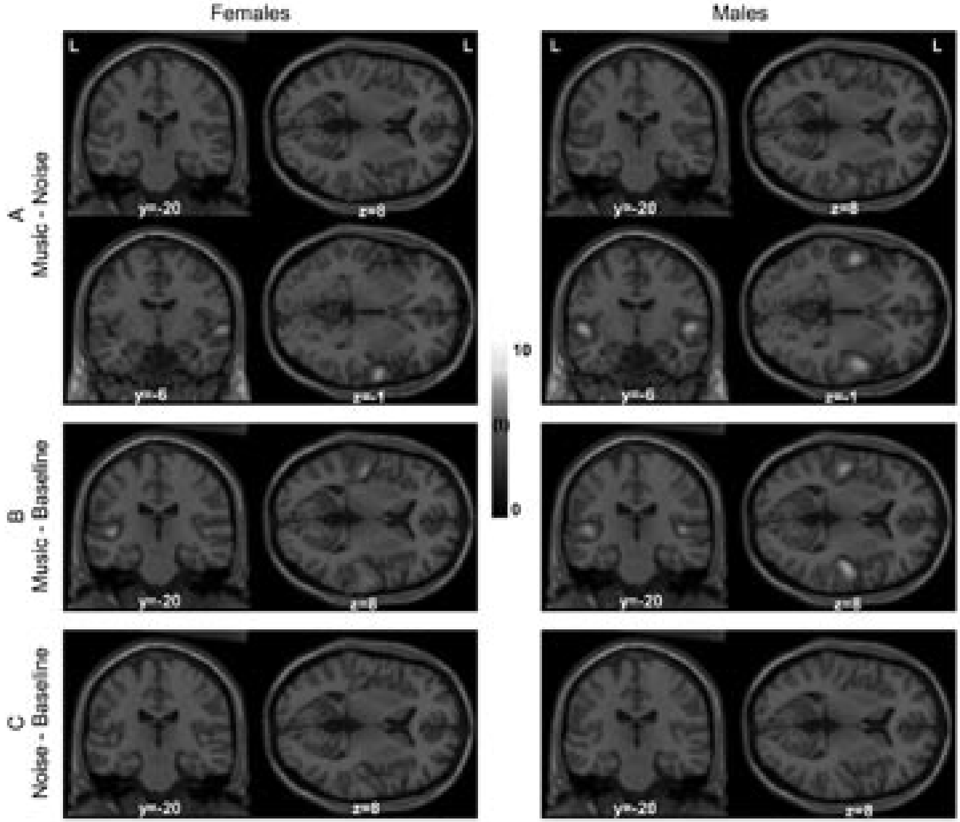

Figure 1. Full-color in appendix. Spatial distribution of significant increases in brain activation in men and women when comparing the auditory processing of noise, music and a baseline. Activations are superimposed on an anatomical MRI template of SPM2. Clusters are significant at $p<0.05$ FDR corrected for multiple comparisons. L=left hemisphere, y=-20 and y=-6 means a coronal plane respectively 20 and 6 mm posterior to the anterior commissure, z=8 means a horizontal plane 6 mm dorsal to the anterior commissure, z= -1 means a horizontal plane 1 mm ventral to the anterior commissure. (A) Contrasting music with noise, women showed activation in the secondary auditory areas only, whereas men showed activation in both PAC and secondary auditory areas. (B) Comparing music to the baseline, both women and men showed bilateral activation in the PAC and secondary auditory areas. (C) Comparing noise to the baseline, women showed bilateral activation in the PAC. In men, on the other hand, no significant activation was found. The differences between men and women in panels A and C are significant (see Table 2).

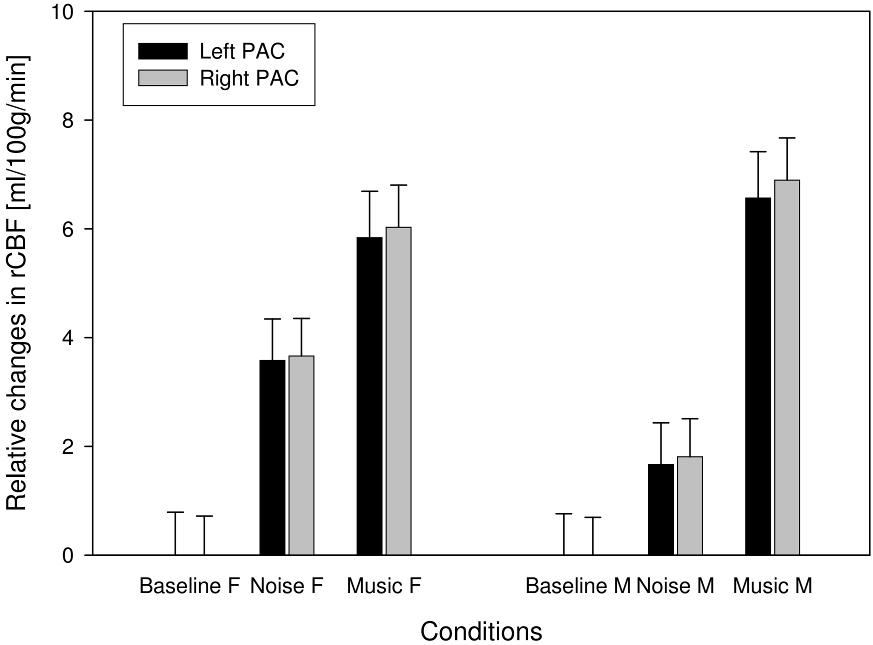

Figure 2. Regional cerebral blood flow relative to the baseline of each group, based on all voxels in the left and right PAC (with a global mean flow of 50 ml/100g/min). Error bars indicate the 90 % confidence interval of the mean across subjects per condition, the confidence interval of the baseline is also given. F=Females, M=Males.

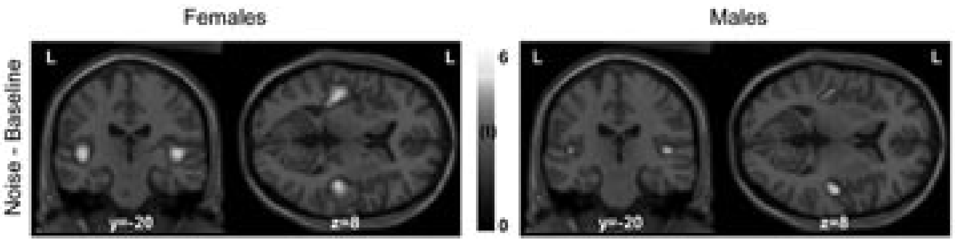

Figure 3. Full-color in appendix. Spatial distribution of significant increases in brain activation in men and women for the comparison of noise to the baseline. Clusters are significant at $p<0.01$ uncorrected for multiple comparisons. L=left hemisphere, y=-20 means a coronal plane 20 mm posterior to the anterior commissure, z=8 means a horizontal plane 6 mm dorsal to the anterior commissure. In contrast to Figure 1 C, at an uncorrected level men do show activation in PAC, but it is much smaller than in the female group.

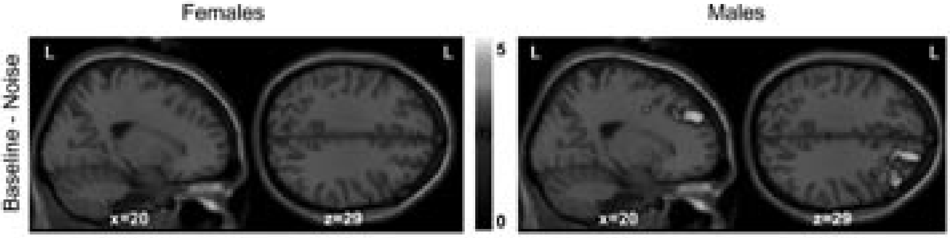

Figure 4. Full-color in appendix. Spatial distribution of significant decreases in brain activation in men and women for the comparison of noise to the baseline. Clusters are significant at $p<0.05$ FDR corrected for multiple comparisons. x=20 means a sagittal plane 20 mm on the right of the anterior commissure, z=29 means a horizontal plane 29 mm dorsal to the anterior commissure. Only men showed a significant deactivation in the dorsolateral prefrontal cortex.

		Side	Region	Talairach Coordinates x	y	z	Number of Voxels	t-value
Music vs Noise	**Females**	Right	BA 22	61	-6	-1	1459	7.77
		Left	BA 22	-51	-10	-1	310	5.02
	Males	Right	BA 41, 42, 22	52	2	-3	3234	7.87
		Left	BA 41, 42, 22	-51	-8	0	2190	7.87
Music vs Baseline	**Females**	Right	BA 41, 42, 22	57	-4	-1	2750	8.85
		Left	BA 41, 42, 22	-48	-17	3	1866	7.97
	Males	Right	BA 41, 42, 22	51	-10	2	2475	10.36
		Left	BA 41, 42, 22	-48	-12	1	2306	8.67
Noise vs Baseline	**Females**	Right	BA 41	46	-21	5	446	6.49
		Left	BA 41	-40	-23	5	463	6.24
	Males	No suprathreshold clusters						
Baseline vs Noise	**Females**	No suprathreshold clusters						
	Males	Right	BA 9	20	50	29	968	5.20

Table 1. Overview of brain areas with statistically significant cerebral blood flow changes. The region, covered by the whole cluster and noted in Brodmann areas, and the number of voxels in the cluster are described (Brodmann, 1909). Only the stereotaxic (Talairach) coordinates and t-value of the maximum of the cluster are given. The significance threshold was $p<0.05$ FDR-corrected for multiple comparisons, extent threshold 8 voxels, voxel size 2x2x2 mm. Brain regions were identified using the Talairach atlas and the stereotactic atlas of the human brain of Mai et al. (Talairach and Tournoux, 1988; Mai et al., 1997).

		P-value	
		Left PAC	Right PAC
Music vs Noise	Females	**0.005***	**0.001***
	Males	**<0.001***	**<0.001***
	Females minus males	0.984	0.992
	Males minus females	**0.016***	**0.008***
Music vs Baseline	Females	**<0.001***	**<0.001***
	Males	**<0.001***	**<0.001***
	Females minus males	0.721	0.779
	Males minus females	0.279	0.221
Noise vs Baseline	Females	**<0.001***	**<0.001***
	Males	**0.016***	**0.005***
	Females minus males	**0.042***	**0.034***
	Males minus females	0.958	0.966

Table 2. Region of interest analysis of the left and right primary auditory cortex (PAC). One-sided statistical significance for various contrasts was tested for men and women separately as well as for the differences between both. * Significant at $p<0.05$

Discussion

Our data demonstrate a sex difference in regional cerebral blood flow in the left and right primary auditory cortex (PAC) when comparing auditory processing of music and noise. The PAC was more activated by music than by noise in both men and women. But this difference between the two stimuli was significantly higher in men than in women. To determine whether this sex difference can be attributed to the processing of music, noise or both, we compared the two stimuli with a baseline of no auditory stimulation. Comparing music with the baseline resulted in extensive activation of the primary and secondary auditory cortex in both sexes, but no significant sex difference was found. On the other hand, a sex difference was detected in the processing of noise, because females activated their PAC significantly more than males. The finding that sex differences in auditory processing can already be detected at the level of the primary cortex is very important, because it is often assumed that sex differences act exclusively upon higher-order cortical areas.

The question is whether this sex difference is caused by the experimental conditions or by other factors like anatomical differences or methodological errors. The reported differences in activation of the PAC stand or fall by a correct identification of this area in the region of interest analysis. Several authors reported substantial intersubject variability in size and location of the PAC (Penhune et al., 1996;Leonard et al., 1998;Morosan et al., 2001;Rademacher et al., 2001b, 2002). To overcome this problem of variability in size and location of the PAC, we employed linear resizing and shearing as well as non-linear warping of the brain to normalize the individual brains into a standardized stereotactic frame. In addition, a Gaussian smoothing filter of 12 mm was used to remove residual variance in brain structure that remains after the stereotactic normalization. Furthermore, we used probability maps, based on the cytoarchitecture of 10 subjects, to identify the PAC (Morosan et al., 2001; Rademacher et al., 2001b; Eickhoff et al., 2005). Other studies suggested that the volume of the PAC is bilaterally larger in females than in males (Rademacher et al., 2001a). It is therefore necessary that the region of interest depicts the PAC of both men and women. This is the case, because the probability maps of the SPM Anatomy toolbox are based on the cytoarchitecture of 5 male and 5 female brains (Morosan et al., 2001; Rademacher et al., 2001b; Eickhoff et al., 2005). For these reasons we believe that possible intersubject or intergroup differences in size and location of the PAC do not bias our results.

If the reported sex and contrast dependent differences in rCBF patterns are not caused by underlying anatomical differences, metabolic differences or methodological errors, they must have been induced by the experimental stimulus. During the baseline condition subjects had to lie quietly in the scanner and no auditory stimulus was applied. Without auditory stimulation and a specific task, the variance in rCBF might increase, resulting in less statistical power when comparing conditions to the baseline. However, as shown in Figure 2, the confidence interval for the model parameters was very similar for the three conditions. In addition, the confidence interval was also very similar for the two sexes. This means that the different contrasts tested have similar statistical power. Considering the significant sexual dichotomy in the processing of music versus noise and the results when comparing either the music or noise with the baseline condition, we conclude that males and females differ in the processing of noise. Thus our data demonstrate a sexual dichotomy in auditory processing. But which mechanism could explain this sexual dichotomy? A key to answering this question is the role of the prefrontal cortex, which we found to be deactivated in men during listening to noise. In humans, the prefrontal cortex is engaged in diverse cognitive processes including cognitive control, working memory and attention (Miller et al., 2001). For example, Gisselgård et al. (2003, 2004) investigated the influence of irrelevant speech on working memory tasks and revealed a functional link between auditory and prefrontal regions. Tzourio et al. (1997) demonstrated that prefrontal areas are engaged in auditory tasks that involve sustained or selective auditory attention. In the present study, no explicit (attention-) task was implemented. Subjects lay passively in the scanner and were instructed to listen to the auditory stimuli. While listening to an insignificant stimulus like noise, males deactivated the prefrontal attention areas as compared to silence. Females, on the other hand, had no deactivation of the attention areas and had a higher activation in the primary auditory cortex. Deactivation of the prefrontal regions was only seen in the right hemisphere, which is consistent with Tzourio et al. (1997), who stated that a right hemisphere dominance exists for attention. The present results suggest a relationship between activation of PAC and prefrontal cortex. From literature, anatomical evidence exists concerning auditory-prefrontal connections. Studies on monkeys have shown that the prefrontal cortex is reciprocally connected with auditory association areas (i.e. belt and parabelt in the monkey brain) (Barbas and Mesulam, 1985). The secondary and primary auditory areas are reciprocally connected (e.g. Kaas & Hackett, 1998). More recent studies on monkeys identified two auditory-prefrontal processing streams: a dorso- and ventrolateral auditory stream (Romanski et al.,1999a; 1999b; Romanski and Goldman-Rakic, 2002). Although, one should be cautious when comparing human and non-human primate brains, a similar organization of several parts of the human and monkey prefrontal cortex has been reported (Petrides and Pandya, 2001; Öngür et al., 2003,).

To summarize, we know from literature that the auditory and prefrontal regions are anatomically and functionally linked and our data show a sexual dichotomy in the (de)activation of both regions. Apparently, the male and female brains handle an insignificant stimulus like noise differently and we propose that this is done by a different engagement of the auditory-prefrontal attention network. Namely, differences in attention result in a different deactivation of the right prefrontal cortex, which in turn modulates the activation of the PAC and thus explains the found sex differences in the activation of the PAC. This corresponds with previous findings that sex differences exist in the frontal-temporal network, namely males have higher intrahemispheric functional connectivity of frontal and temporal areas than females (Gootjes et al., 2006). And it is also known from ERP-studies that sex differences exist in orienting attention to auditory stimuli (Nagy et al., 2003). It must be noted that even though our data indicate differences in the auditory-system, no independent behavioral data regarding the attention levels during scanning are available. Hence the present experimental design allows us only to speculate about the correlation between the different deactivation of the prefrontal cortex and differences in attention. Further research is needed to fully clarify the role of attention on PAC activation and to determine whether our results can be repeated.

To our knowledge, this is the first time that a sexual dichotomy in the function of the PAC is demonstrated. Previously, a sexual dichotomy has been reported in auditory feedback loops although they were found in the corticofugal auditory network. For example, men show more suppression of repeated acoustic stimuli than females. This sex difference in auditory gating is probably the result of differential neuronal inhibition to repeated stimulation (Hetrick et al., 1996). Likewise, the stronger spontaneous otoacoustic emissions (SOAE's) in females are thought to originate from a relatively larger amount of efferent inhibition in males (McFadden, 1993). This efferent innervation would start in the olivary complex and terminate in the outer hair cells of the cochlea (MacFadden, 1993).

Although the present sexual dichotomy would be consistent with the concept of evolutionary advantages in a hunter-gatherer society (e.g. Kimura, 1999) where the inhibition of constant irrelevant stimuli in men may facilitate them to focus their attention to a single task i.e. hunting, this concept remains speculation.

In conclusion, a very significant sexual dichotomy was found in the activation of the PAC with different types of acoustic stimuli (noise and music) together with sex differences in deactivation of prefrontal areas. It is known that the auditory and prefrontal regions are anatomically and functionally linked and the prefrontal cortex is engaged in auditory attention tasks. Hence we hypothesize that differences in attention result in a different involvement of the right prefrontal cortex, which in turn modulates the activation of the PAC. This shows that sex influences brain activity already at the level of primary sensory cortex and that in functional imaging studies on primary sensory cortical areas, sex can not be ignored.

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